The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 37

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

MAILED

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U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ALLISON HUBEL

Appeal No. 2004-1510
Application No. 09/458,862

HEARD: November 18, 2004[1]

Before SCHEINER, MILLS, and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-8, 11, 12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-58, the claims on appeal in this application.[2]

[1] The oral hearing of November 18, 2004 was conducted telephonically.

[2] Appellant submitted an Amendment with the Brief cancelling claims 35 and 36 and adding claims 59 and 60. Paper No. 27. The examiner provided no indication in the Answer whether this amendment was entered or considered thus, the appeal was returned to the examiner by the Board to clarify the pending claims on appeal. The examiner did not comply. The Board also requested that a revised Appendix to the Brief be filed which reflected pending claims. Paper No. 31. Appellant subsequently submitted a revised Appendix I to the Brief, via fax. Paper No. 32. It appears that the argument section of the Brief was not revised to correspond to the claims as they appear in revised Appendix I. It also appears that the examiner erroneously indicated

Claims 1, 26 and 37 are illustrative of the claims on appeal and appear below.

Remaining pending claims appear in the attached Appendix to the Brief.

1. A cryopreservation medium comprising a balanced electrolyte solution incorporating at least one cryoprotective agent that is arabinogalactan, or a biological or functional equivalent thereof, which agent is present in an amount of 1% w/v to 40% w/v, and freshly isolated lymphocytes, hematopoietic stem cells, lymphocytes which are modified *ex vivo*, or a combination thereof, wherein the medium does not comprise dimethylsulfoxide or serum, and wherein the arabinogalactan, a biological or functional equivalent thereof, in the medium results in a high post-thaw survival rate for the freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are modified *ex vivo*.

26. A method for preserving cells comprising:
(a) contacting cells with a cryopreservation medium comprising a balanced electrolyte solution and at least one cryoprotective agent that is arabinogalactan, or a biological or functional equivalent thereof, in an amount of 1% w/v to 40% w/v, to yield a cell suspension, wherein the cells are freshly isolated lymphocytes, hematopoietic stem cells, lymphocytes which are modified *ex vivo*, or a combination thereof, wherein the medium does not comprise dimethylsulfoxide or serum, and wherein the arabinogalactan in the medium results in a high post-thaw survival rate for the freshly isolated lymphocytes, hematopoietic stem cells, or lymphocytes which are modified *ex vivo*; and

(b) freezing the cell suspension to yield a frozen cell suspension.

37. A cryopreservation medium comprising a balanced electrolyte solution, at least one cryoprotective agent that is arabinogalactan, or a biological or functional equivalent thereof, in an amount of 1% w/v to 40% w/v, and freshly isolated lymphocytes, hematopoietic stem cells, lymphocytes which are modified *ex vivo*, or a combination thereof, wherein the medium does not comprise dimethylsulfoxide or serum, and wherein the balanced electrolyte solution is selected from the group consisting of lactated Ringer's solution, PlasmaLyte-A™, Normosol-R™, Veen-D™, Polysal®, and Hank's balanced salt solution.

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in the Answer, that the original claims submitted with the Brief were correct. In any event, in view of appellant's submission of a revised version of the claims on appeal and acceptance of these claims by the examiner, we have assumed for purposes of this appeal that the revised Appendix I to the Brief (Paper No. 32) is reflective of the claims on appeal and that the original Amendment filed with the Brief was not entered by the Examiner.

The prior art reference cited by the examiner is:

Oliver et al (Oliver)	WO 97/35472	Oct. 2, 1997

Grounds of Rejection

Claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-58 stand rejected under 35 U.S.C. 103(a), as obvious over Oliver.

Claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-52 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement throughout the claim scope.

The rejection of claims 1-3, 7-8, 11, 12, 14, 16, 17, 21-22, 24, 26-28, 30-32, 35-36, 49, 52, 53, 55 and 58 under 35 U.S.C. 103(a) over Oliver is affirmed, but we reverse the rejection with respect to claims 4-6, 19-20, 33-34, 37-44, 47-48, 50-51, 54, 56-57. We reverse the rejection of the claims under 35 U.S.C. 112, first paragraph, for lack of enablement.

Claim Grouping

According to Appellant, with respect to the rejection of the claims under 35 USC 103(a), claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 31, 33-36, 53 and 55 stand or fall together in Group I; claims 26-28, 30, 32, 49-52 and 58 stand or fall together in Group II; claims 37-48 stand or fall together in Group III; claims 54 and 56 stand or fall together in Group IV; claim 57 stands alone as Group V for purposes of this appeal. Brief, page 6. Therefore, we select claim 1 as representative of Group 1; claim 26 as

representative of Group 2; claim 37 as representative of Group III. The rejections of Groups IV and V are reversed.

DISCUSSION

35 U.S.C. 103(a)

Claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-58 stand rejected under 35 U.S.C. 103(a), as obvious over Oliver.[3]

It is the examiner's position that Oliver (Answer, pages 3 and 4):

> discloses a cryopreservation medium comprising a balanced salt solution, suitable for a specific cell type (page 6, lines 25-26), arabinogalactan present in the range of between 5 and 70%, preferably between 14 and 20% (wt./vol.) (page 7, lines 4-10). The WO patent also teaches on page 7 that the presence f [sic] DMSO is optional and that the cryopreservation medium can include glycerol. .... Although lymphocytes are not specifically disclosed by the WO patent, the term "somatic cells" encompasses lymphocytes and a person having ordinary skill in the art at the time the instant invention was made would have been motivated to use the cryopreservation medium disclosed by the WO patent for any somatic cells, including lymphocytes especially since the WO patent discloses that two of the most widely used cryopreservation agents, DMSO and glycerol, are damaging to thawed cells" (page 2, lines 30-31 and page 3, lines 1-2) but that the presence of arabinogalactan in the media reduces cellular damage (page 8, lines 5-11).

[3] The Examiner refers to Oliver in the Answer as WO 97/35472 or WO Patent.

Claims 1 and 26

Claims 1 and 26 are of similar scope. Claim 1 is directed to a cryopreservation media of specific composition and claim 26 is directed to a method of preserving cells with the cryopreservation media of claim 1. Thus, we address these claims together. We agree that the examiner has provided sufficient evidence to support a prima facie case of obviousness of claims 1 and 26. Claims 2-3, 7-8, 11, 12, 14, 16, 17, 21-22, 24, 27, 28, 30, 31, 32, 35-36, 49, 52, 53, 55 and 58, fall with claims 1 and 26.

Oliver states that arabinogalactan provides a useful low cost alternative to the use of DMSO or serum in cell cryopreservation media. Page 6, lines 17-18. Oliver indicates that, "the presence of arabinogalactan in the media, alone or in combination with other cryoprotective agents, reduces cellular damage due to the cryopreservation process and increases post-thaw viability." Page 5, lines 5-8. Oliver also states that "removal of a cell permeating or cell damaging cryoprotectant such as DMSO or glycerol can be implemented by dilution with culture medium or by cell washing..." Pages 9, lines 9-11. Oliver thus teaches that the presence of arabinogalactan protects the viability of cells in the medium during the process of freezing, storing and thawing. See Abstract.

The arabinogalactan medium of Oliver may be used for cryopreservation of somatic cells, including somatic cells derived from the circulatory system (Claim 19), immune cells (page 10, line 4 and page 11, line 30) and blood (Page 10, line 4). Furthermore, Oliver provides for a preferred arabinogalactan concentration of between

14 and 20%. Page 7, lines 7-9. A medium containing a balanced salt solution is also disclosed. Page 6, line 25.

Appellant argues (Brief, pages 12 and 13)

> [t]he only data provided in the WO 97/35472 [Oliver] specification is for seven lines of immortalized mammalian cells ... These mammalian cells include three rodent epithelial cell lines, a mink fibroblast line, a bovine endothelial cell line..., and a murine pre-neoplastic mammary cell line...
>
> No hematopoietic cells are represented in the seven lines of cells disclosed in WO 97/35472. Moreover, blood is known to include erythrocytes and leukocytes, and that the major classes of leukocytes are lymphocytes, monocytes, neutrophils, eosinophils, and basophils ...

Appellant further points to the Declarations under 37 CFR § 1.132 of Drs. Hubel and Bischof filed in the application and data present in Tables 3 and 4 of appellant's specification in support of patentability of the claimed invention. Brief, pages 12 and 15.

While we have carefully considered the Declarations of Drs. Hubel and Bischof, we do not find they provide sufficient evidence to overcome the examiner's prima facie case of obviousness with respect to claims 1 and 26. Both Declarations state that different cell types have their own unique biophysical characteristics, including water content, which affects their cooling rates during cryopreservation (Hubel, paras. 8, 10; Bischof, para. 4).[4] On this basis appellant and the Declarants argue that Oliver,

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[4] Rapid cooling is indicated in the Hubel Declaration to not allow sufficient time for water to leave the cell in response to the increase in extracellular solution concentration resulting from the removal of water in the form of ice (due to freezing). According to Dr. Hubel, undercooling of the cell relative to the extracellular solution results in intracellular ice formation, a lethal event, while slow cooling can result in

describing a general cryopreservation medium, would not have provided one of ordinary skill in the art with a reasonable expectation of success in cryopreserving freshly isolated lymphocytes, hematopoietic stem cells or ex vivo modified lymphocytes (Bischof, para. 6; Hubel, para. 11).

Nevertheless, neither Declarant has provided evidence that supports the assertion that one skilled in the art would not have had a reasonable expectation that arabinogalactan would not work as Oliver suggested to preserve different cell types. Dr. Hubel's declaration demonstrates the effect of different glycerol concentrations in a cryopreservation medium on post thaw survival and cooling rate of red blood cells, but the declarant does not explain how this demonstration would have any bearing on how one skilled in the art would expect different cell types to fare if preserved in identical media. No unexpected result is evidenced.

Nor are we convinced with respect to the data presented in Tables 3 and 4 of the specification. To begin, the data in Tables 3 describes a comparison of the post-thaw viability of activated lymphocytes versus cultured cells using a culture medium and arabinogalactan, glycerol and Normosol-R. According to the specification lines 22-25, the results in table 3 indicate "that there is no statistically significant difference in post-thaw viability of the cultured cells and activated cells." Thus, while the two cell types are arguably different, it is not seen how this data supports the proposition that one skilled in the art would have expected different cell types to fare differently if preserved

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excessive dehydration of the cell which is also damaging to the cell (Hubel, para. 7).

in identical media. The results were not statistically significant.

Table 4 of the specification compares genetically modified cells from donors with MPS II with cells from normal donors. The overall recovery of genetically modified cells from a donor with MPS II was less than observed for freshly isolated cells from a normal donor. However when the standard of error is considered for this data, the results are essentially similar. Therefore, it is not seen how this data supports the proposition that one skilled in the art would have expected different cell types to fare differently if preserved in identical media.

Table 5 (specification, page 37) looks at the colony recovery rate of only one cell type, mononuclear cells, in two different media. Therefore, it is not seen how this data supports the proposition that one skilled in the art would expect different cell types to fare differently if preserved in identical media.

Appellant also asks consideration of two references of record. Appellant argues that Sputtek notes that the conditions employed to freeze red blood cells were suboptimal for the preservation of viable white blood cells. Brief, page 15. However, a review of this publication, indicates that "[i]n the case of frozen blood, i.e., red blood cells cryopreserved according to the high glycerol technique and subsequently deglycerolized and washed, it was shown that residual lymphocytes could not be completely eliminated, and that about 60% of the cells remained viable (TPB exclusion)." P. 127. In another study discussed in Sputtek, it was found that "a significant number of lymphocytes and macrophages from rat survived freezing up to 20

K/min (10 to 40%), whereas negligible levels were detected at 75 and 200 K/min." P. 127.

While appellant may characterize such results as "suboptimal" the Sputtek publication does not show that one of ordinary skill in the art would have expected that lymphocytes would not survive in conditions which are appropriate for red blood cells, or that a cryopreservation media for blood cells as taught by Oliver would not be appropriate for lymphocytes. Thus, we are not persuaded by this evidence.

Appellant argues that Hubel (Transfusion Med. Rev.) discloses that membrane permeability parameters for a number of blood cells types including lymphocytes were found to be distinctive. Brief, page 15. Appellant fails to indicate how one of ordinary skill in the art would understand that membrane permeability has any bearing on whether or not the specific media of Oliver would work with lymphocytes.

Appellant also references a Rule 132 Declaration executed by Dr. Hubel on August 27, 2001 which states that granulocytes (a blood cell) cannot be cryopreserved at all and the neutrophils, eosinophils and basophils are included in granulocytes. Brief, page 14. Hubel Declaration, paragraph 5. To begin, this statement of Dr. Hubel is not supported by evidence of record. Secondly, Oliver, which uses a media similar to the claimed media states that the medium works for a wide range of somatic cells, including blood cells (Oliver, page 10).

Appellant has failed to present sufficient evidence to rebut the examiner's prima facie case of obviousness in view of Oliver. Thus, appellant has not established by a preponderance of the evidence that one skilled in the art would expect different cell types to fare differently if preserved in identical media, in view of the disclosure of Oliver.

In sum, we do not find appellants have presented sufficient argument and evidence to rebut the examiner's prima facie case of obviousness with respect to claims 1 and 26. Claims 2-3, 7-8, 11, 12, 14, 16, 17, 21-22, 24, 27, 28, 30, 31, 32, 35-36, 49, 52, 53, 55 and 58, fall with claims 1 and 26.

Group II

We do not agree, however, that the examiner has presented sufficient evidence to support a prima facie case of obviousness with respect to claims 4-6, 19-20, 33-34, 50-51, 54 and 56-57. Although glycerol is indicated in Oliver to be an optional cryoprotective agent ingredient, Oliver states that DMSO and glycerol "are damaging to thawed cells due to osmotic complications and must be removed from cells post-thaw via rinsing and centrifugation." Oliver, paragraph bridging pages 2-3.

Thus, Oliver essentially provides a teaching away from the inclusion of glycerol in a cryoprotective agent. We do not find sufficient evidence has been presented to show unpatentability of a preservation media for lymphocytes comprising both arabinogalactan and glycerol. In particular, Table 5 of appellant's specification shows

that hematopoietic progenitor cells can be effectively cryopreserved in solutions containing arabinogalactan, and shows a significant improvement in colony recovery rates when the cryopreservation medium contains both arabinogalactan and glycerol. Specification, page 34. Nor do we find that Oliver describes the particularly claimed amounts of glycerol in claims 54, 56 and 57. Furthermore, the Hubel Declaration, paragraph 8, would appear to show that viability of red blood cells upon cryopreservation is influenced by the amount of glycerol present. Moreover, the examiner acknowledges that the prior art, Oliver, teaches that DMSO and glycerol are damaging to thawed cells.

We reverse the rejection of claims 4-6, 19-20, 33-34, 50-51, 54, 56-57 under 35 U.S.C. 103(a) in view of Oliver.

Group III, Claim 37

Claim 37 is directed to a cryopreservation medium comprising a balanced electrolyte solution, at least one cryoprotective agent that is arabinogalactan, or a biological or functional equivalent thereof, in an amount of 1% to 40% w/v and freshly isolated lymphocytes, hematopoietic stem cells, lymphocytes which are modified ex vivo, or a combination thereof, wherein the medium does not comprise dimethylsulfoxide or serum, and wherein the balanced electrolyte solution is selected from the group consisting of lactated Ringer's solution, PlasmaLyte-A™, Normosol-R™, Veen-D™, Polysal®, and Hank's balanced salt solution. Brief, page 17.

Appellant argues that Oliver fails to disclose or suggest a cryopreservation medium wherein the balanced electrolyte solution is selected from the group consisting of lactated Ringer's solution, PlasmaLyte-A™, Normosol-R™, Veen-D™, Polysal®, and Hank's balanced salt solution. Brief, page 17.

The examiner acknowledged the appellant's separate grouping of the claims but failed to respond to this specific argument of appellant in the Answer. It is clear that Oliver describes a cryopreservation media including arabinogalactan and a balanced salt solution. We do not find, however, that the examiner has presented any evidence to support a nexus or equivalency in the art between the DMEM (Dulbecco's Modified Eagle Medium) or a balanced salt solution described in Oliver and the claimed balanced electrolyte solution selected from lactated Ringer's solution, PlasmaLyte-A™, Normosol-R™, Veen-D™, Polysal®, and Hank's balanced salt solution. Each of the claimed salt solutions has a different and distinct composition. It would appear apparent from the art that components of a cryopreservation medium have the potential to affect the stability of cryopreservation. No argument or evidence has been presented by the examiner that the additional components of the claimed balanced salt solutions would not have been considered by those of ordinary skill in the art to affect cryopreservation characteristics.

Patent examiners, in relying on what they assert to be general knowledge to negate patentability on the ground of obviousness, must articulate that knowledge and place it of record, since examiners are presumed to act from the viewpoint of a person

of ordinary skill in the art in finding relevant facts, assessing the significance of prior art, and making the ultimate determination of the obviousness issue. Failure to do so is not consistent with either effective administrative procedure or effective judicial review, examiners cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which they rely. See In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002). Thus, it is improper to rely on the "common knowledge and common sense" of a person of ordinary skill in art to find an invention obvious over a combination of prior art references, since the factual question of motivation to select and combine references is material to patentability, and cannot be resolved on subjective belief and unknown authority. In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002).

In view of the above, and withholding comment as to the patentability of these claims, we do not find the examiner has set forth a prima facie case of obviousness with respect to claim 37 or claims depending from it. The rejection of claims 37-44 and 47-48 is reversed.

35 U.S.C. 112, first paragraph

Claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-58 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement throughout the claim scope.

The examiner argues that while the specification is enabling for arabinogalactan, it does not reasonably provide enablement for a biological or functional equivalent thereof. Answer, page 2. The examiner further argues that the terminology "biological or functional equivalent thereof" encompasses derivatives of arabinogalactan in addition to compounds which are structurally unrelated to arabinogalactan but which possess a biological function which is equivalent to arabinogalactan. Answer, page 3.

The examiner reaches this conclusion based on the term "includes" in the definition of arabinogalactan in the specification. The examiner finds that the term "includes" means that the definition of a biological or functional equivalent of arabinogalactan is not limited to those set forth on page 4 of the specification but encompassess compounds which are structurally unrelated to arabinogalactan.

In our view, the examiner reads the definition of the term "arabinogalactan, a biological or functional equivalent thereof" too broadly. The specification, page 4, states that, "'arabinogalactan, a biological or functional equivalent thereof' includes naturally occurring or synthetic arabinogalactan, portions of arabinogalactan, such as degradation products or synthetic arabinogalactan and chemically ... or biochemically modified arabinogalactan or portions thereof which have been modified by methods available in the art..." The specification does not speak of other types of functional equivalents of arabinogalactan which are structurally unrelated to arabinogalactan.

Furthermore, appellant, in the Brief pages 7-8, would also appear to limit the interpretation of this phrase to the definition set forth on page 4 of the specification. Thus, appellant has created a prosecution history estoppel[5] as to what she considers to be biological and functional equivalents of arabinogalactan within the scope of the claims.[6] Thus, we do not agree with the examiner that appellant's claims encompass compounds which are structurally unrelated to arabinogalactan. The rejection of the claims for lack of enablement is reversed.

CONCLUSION

The rejection of claims 1 and 26 is affirmed. Claims 2-3, 7-8, 11, 12, 14, 16, 17, 21-22, 24, 27, 28, 30, 31, 32, 35-36, 49, 52, 53, 55 and 58, fall with claims 1 and 26. We reverse the rejection of claims 4-6, 19-20, 33-34, 37-44, 47-48, 50-51, 54 and 56-57 as obvious in view of Oliver.

The rejection of claims 1-8, 11-12, 14, 16, 17, 19-22, 24, 26-28, 30-44 and 47-58 under 35 U.S.C. 112, first paragraph, for lack of enablement throughout the claim scope is reversed.

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[5] Prosecution history estoppel requires that patent claims be interpreted in light of the proceedings before the Patent and Trademark Office (PTO). As stated by this court in Hughes Aircraft Co. v. United States, 717 F.2d 1341, 1362, 219 USPQ 473, 481 (1983): "The estoppel applies to claim amendments to overcome rejections based on prior art, * * * and to arguments submitted to obtain the patent."

[6] We also note that appellants stipulated as to this claim scope in the telephonic hearing of November 18, 2004.

is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

TONI R. SCHEINER
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

LORA M. GREEN
Administrative Patent Judge

) BOARD OF PATENT
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